Original Report

Use of Itraconazole in the Treatment of Mucocutaneous Leishmaniasis: A Pilot Study

Valdir S. Amato, MD;* Alexandre R. S. Padilha, MD;* Antônio C. Nicodemo, PhD;* Maria I. S. Duarte, PhD;† Mario Valentini, MD;‡ David E. Uip, PhD;* Marcos Boulos, PhD;* and Vicente Amato Neto, PhD*

ABSTRACT

Objectives: Mucocutaneous leishmaniasis is widely distributed in Brazil, with *Leishmania (Viannia) braziliensis* being the major etiologic agent. The currently recommended therapy is limited by its parenteral use, high toxicity, and variable efficacy. A clinical pilot study was conducted to analyze itraconazole as an oral alternative for the treatment of mucocutaneous leishmaniasis.

Methods: Ten patients were enrolled to receive 4 mg/kg per day (up to 400 mg/d) itraconazole for 6 weeks on an outpatient regimen. Diagnosis was based on clinical otorhinolaryngologic examination, followed by a specific serologic reaction, the Montenegro test and pathologic analysis with immunohistochemical reaction. Healing of the lesions was confirmed by clinical otorhinolaryngologic examination. Side effects were monitored by general clinical assessment, hemoglobin determination, leukocyte counts, and liver function tests, all performed before, during, and 1 month after the end of treatment.

Results: Six of 10 patients presented healed lesions 3 months after treatment, with a sustained therapeutic response for at least a median period of 14.5 months (range, 12–18 mo). Side effects were not observed.

Conclusions: This pilot study demonstrated that itraconazole can be an effective and well-tolerated alternative for the treatment of mucocutaneous leishmaniasis. Further randomized studies and double blind controlled trials are needed to assess the benefits of this drug in the treatment of mucocutaneous leishmaniasis.

Key Words: *itraconazole, mucocutaneous leishmaniasis, mucosal leishmaniasis, treatment*

Int J Infect Dis 2000; 4:153–157.

*Department of Infectious and Parasitic Diseases, †Laboratory of Pathology of Infectious Diseases, and ‡Department of Ophthalmology and Otorhinolaryngology, Clinics Hospital of University of São Paulo, School of Medicine, São Paulo, Brazil.

Received: April 27, 1999; Accepted: August 25, 1999.

Address correspondence to Dr. Valdir Amato, Alameda Gabriel Monteiro da Silva, 429, CEP: 01441-000, São Paulo, Brazil. E-mail: valdirsa@netpoint.com.br.

Leishmaniasis is a disease that illustrates the extent to which human action in the transformation of ecosystems can result in human disease. What previously was a cycle without human participation has now become a human disease in several regions of the world. A total of 12 million cases has been estimated worldwide, with increasing numbers in periurban regions.[1] In Brazil, approximately 200 thousand cases of American tegumentary leishmaniasis (ATL) and 23 thousand cases of visceral leishmaniasis have been reported between 1980 and 1993.[2]

Specifically concerning ATL in Brazil, the most prevalent species of infecting agents are *Leishmania (Leishmania) amazonensis, Leishmania viannia guyanensis,* and *Leishmania viannia braziliensis,* whereas the vectors are sandflies of the genera *Lutzomyia* and *Psychodopygus*. Particularly important is *L. viannia braziliensis,* present in all regions of the country and causing the mucocutaneous form of the disease.[2,3]

In the Americas, ATL occurs in three clinical forms: cutaneous, diffuse cutaneous, and mucocutaneous. In mucocutaneous leishmaniasis (MCL), after a period of incubation of 15 to 60 days, a pruriginous nodule arises that progresses to a round or oval, large and shallow ulcer with raised borders, purplish in color, and only slightly painful. One or several lesions may occur. Spontaneous cure of cutaneous lesions has been reported in the literature.[4] Involvement of the mucosa of the nasopharynx, oropharynx, larynx, or trachea is a complication that may cause destruction of tissues, difficulty in eating because of dysphagia, or even tracheomalacia, with patient death occasionally occurring due to aspiration or respiratory obstruction.[5]

Pentavalent antimonials are the drugs of preference for the treatment of ATL, although their effectiveness is limited in MCL, and they sometimes have significant toxicity and side effects.[6] Pentamidine and amphotericin B are alternative drugs commonly recommended; however, they may have significant side effects and also require parenteral administration.[7] Among the other drugs used for the treatment of MCL are liposomal amphotericin, aminosidine sulfate, and the combination of allopurinol and interferon-gamma with antimonials.[8–11]

A drug administered orally, with lower toxicity and adequate to the epidemiologic reality of MCL, would be of considerable benefit. There has been a growing interest in imidazoles; additionally, the anti-leishmania action of ketoconazole has been demonstrated in vitro.[12] Encouraged by the clinical results obtained with the cutaneous form, in the present study, the authors investigated the oral use of itraconazole for the treatment of MCL, a procedure that, it is believed, previously has not been applied.[13]

PATIENTS AND METHODS

Patients

Ten patients with MCL were followed-up at the Specialized ATL Outpatient Clinic, Section of Infectious and Parasitic Diseases, University Hospital, Faculty of Medicine, University of São Paulo. Data concerning to sex, age, and symptoms were obtained from these patients. Each patient gave written consent to participate in the study after being informed in detail about the study and its possible benefits and side effects. The study was approved by the Ethics and Research Committees of the Department of Infectious and Parasitic Diseases of the Faculty of Medicine, University of São Paulo. The inclusion criterion was a diagnosis of MCL based on the parameters described below. The exclusion criteria were pregnancy, the use of any medication for the treatment of MCL during the previous 6 months, and transaminase alterations.

Diagnosis

Diagnosis was based on clinical otorhinolaryngologic evaluation performed by the same specialist to determine the presence of hyperemia, edema, granulation, or septal perforation with an inflammatory aspect on its borders, using indirect or direct laryngoscopy and fibroscopic examination when necessary. The Montenegro skin test and serologic reaction by indirect immunofluorescence were applied. Material obtained from a biopsy of the lesions was submitted to anatomopathologic examination, after staining by hematoxylin-eosin, and to immunohistochemical reaction for *Leishmania* antigens. To exclude other etiologic agents, staining by the Ziehl-Neelsen and Grocott-Gomori methods was also performed.

Drug Regimen

The patients were treated with itraconazole in capsule form for 6 weeks, with a daily dose of 4 mg/kg per day, to a maximum of 400 mg per day, administered in two daily doses at mealtime. The use of the medication and possible side effects were determined every 2 weeks.

Follow-up

Patients were followed-up at the outpatient clinic at 15-day intervals to determine compliance with treatment and the possible occurrence of adverse side effects, such as nausea, vomiting, or diarrhea. Hemoglobin, leukocytes, and serum transaminases were determined before treatment and also at 15-day intervals until the end of treatment. Healing of the mucosal lesions was evaluated by otorhinolaryngologic examination, and was considered to have occurred when the aforementioned otorhinolaryngologic signals had disappeared. These evaluations were repeated monthly until the third month after the end of treatment. To date, the patients have been followed-up on an ambulatory basis by otorhinolaryngologic evaluation to ensure early detection of any possible recurrence.

Response to Treatment

Response to itraconazole treatment was defined as the occurrence of healing of MCL lesions within a maximum of 12 weeks after the end of treatment, characterized by the disappearance of the signs previously described, as determined by otorhinolaryngologic examination and by the absence of disease reactivation during the follow-up period.

RESULTS

Patient data concerning age, sex, and clinical, anatomopathologic, and laboratory findings are presented in Table 1. No patient presented concomitant cutaneous involvement. Ziehl-Neelsen and Grocott-Gomori stains were negative in all of them.

There were no problems concerning tolerance to the medication, and no patient abandoned treatment. With respect to disease antecedents, two patients were hypertensive, one of them taking hydrochlorothiazide and the other propanolol. None of the patients took any other medications in addition to itraconazole and to the antihypertensive drugs taken by these two patients. In the otorhinolaryngologic evaluation during the third month after the end of treatment, 6 of the 10 patients (60%) presented healed lesions with the absence of the clinical signs previously described. Two patients previously found to be refractory to standard treatment schedules presented healing after the use of itraconazole. One of them had not presented any improvement after the use of N-methylglucamine antimoniate and the other one had suffered a relapse after the use of pentamidine isethionate. The data concerning previous therapeutic history and outcome after treatment with itraconazole are described in Table 2. To date, the mean follow-up time without reactivation of the disease for the patients whose lesions were healed by itraconazole has been 14.5 months

Table 1. Patient Characteristics Concerning Age, Sex, Clinical, Anatomopathologic, and Laboratory Data before Treatment with Itraconazole

Patient	Age (yr)	Clinical Examination	Anatomopathologic Examination	Montenegro Reaction	Serology* (IFI)	IHR
1	65	Perforation and hyperemia of NS	Granuloma	+	+	+
2	48	Granulation and perforation of NS	Granuloma	+	+	–
3	63	Perforation and hyperemia of NS	Granuloma	+	+	–
4	44	Perforation and hyperemia of NS	Granuloma and presence of amastigote forms	+	+	+
5	67	Granulation and hyperemia of NS	Chronic infiltrate and intense plasmocytosis	+	+	ND
6	40	Granulation and hyperemia of NS and oropharynx	Chronic infiltrate and intense plasmocytosis	+	+	+
7	80	Perforation and hyperemia of NS	Chronic infiltrate and intense plasmocytosis	+	+	+
8	61	Granulation and hyperemia of NS	Chronic infiltrate and plasmocytosis	+	+	+
9	44	Perforation and hyperemia of NS	Chronic infiltrate and plasmocytosis	+	+	–
10	34	Hyperemia of NS	Chronic infiltrate and plasmocytosis	+	+	ND

*Indirect immunofluorescence reaction (IFI). IHR = immunohistochemical reaction; + = positive; – = negative; ND = not done; NS = nasal septum.

(range, 12–18 mo). Hematologic parameters and liver enzymes monitored during the study were within normal values.

DISCUSSION

In Brazil, mucocutaneous leishmaniasis, caused by *L. viannia braziliensis*, traditionally presents a variable response to treatment with antimonials, with frequent relapses.[14] Few reports are available in the literature about the specific use of itraconazole for treatment of the disease caused by *L. viannia braziliensis*, and no reports exist about the use of the drug for treatment of the mucocutaneous forms.[15] This report describes the experience of 10 patients with MCL treated orally with itraconazole on an outpatient basis.

Studies with antimonials have shown variable efficacy, some of them reporting a success rate of about 60%, with 30% healing maintained after 12 months of follow-up.[3,16,17] Pentamidine and amphotericin B, considered to be second-choice treatments, also present variable results, at times better than those obtained with antimonials, but their toxicity and physiologic difficulties should be considered.[18–20] The same applies to the combination of allopurinol and interferon-gamma with antimonials.[10,11]

Itraconazole has proven action against leishmania in vitro, inhibiting important steps in the development of the protozoon related to ergosterol synthesis and DNA.[21,22] The drug presents excellent bioavailability when administered orally, especially if ingested with food. By being lipophilic, it reaches better tissue concentrations than other imidazoles, including concentration in mucosa and skin, leading to tissue:blood ratios of up to 3:1.[23] The drug is assumed to reach the skin and mucosa through the sebaceous glands and continues to be present in active concentrations in these tissues for up to 2 weeks.[13] Itraconazole previously has been used for the treatment of the cutaneous form of leishmaniasis, also in randomized double blind studies, with a therapeutic success rate ranging from 55% to 70%.[13,15,24,25]

In this study, the MCL diagnosis consisted of typical otorhinolaryngologic examination, serologic reaction, and the anatomopathologic evaluation previously described, which are compatible with findings in such a disease.[26,27] As previously reported, the presence of leishmanial amastigote forms in anatomopathologic evaluation is rare in this clinical presentation, and immunohistochemical reaction sensitivity ranges from 62% to 70%; consequently, its negativity does not exclude a diagnosis of leishmaniasis.[26,28] Even when the parasite is not detected by anatomopathologic examination, or when its antigens are not

Table 2. Therapeutic History and Evolution after Treatment with Itraconazole

Patient	Previous Therapy	Time Since Previous Therapy (mo)	Response to Itraconazole	Follow-up after Itraconazole Treatment (mo)
1	Antimoniate*	108	Healing	18
2	None	None	Failure	3
3	None	None	Failure	3
4	None	None	Failure	3
5	None	None	Failure	3
6	None	None	Healing	14
7	Pentamidine†	14	Healing	12
8	None	None	Healing	14
9	None	None	Healing	14
10	None	None	Healing	15

*N-methylglucamine antimoniate (20 mg/kg/d Sb^v for 30 days).
†Pentamidine isothionate (total dose of 2500 mg).

detected by immunohistochemistry, treatment of MCL can be started based on a compatible clinical picture and on a positive Montenegro skin test and serology by indirect immunofluorescence.[4] In addition, in the present study the researchers searched for fungi by Grocott-Gomori staining, to rule out the presence of another possible etiologic agent for which itraconazole could be therapeutic, and for mycobacteria by Ziehl-Neelsen staining. Both tests were negative in all patients.

Currently, there are no effective healing or cure criteria for evaluating MCL treatment, and this may be why clinical and otorhinolaryngologic evaluations have been used in a large number of studies.[4,8,11,29] It is worth emphasizing that the presence of an inflammatory process, the parasite itself, or its antigens may persist long after successful treatment of MCL, as shown by anatomopathologic examination or by immunohistochemistry of biopsy material.[26,30] Additionally, serologic tests are of questionable usefulness for follow-up after treatment.[31] On the other hand, *L. viannia braziliensis* is a difficult parasite to isolate and maintain in the laboratory, so it has been difficult to make use of this criterion as evaluation of treatment success.[32,33]

In this study, 6 of the 10 patients treated (60%) presented healing of the lesions. Of the six patients who evolved with healing of the lesions, two had previously used standard treatment schedules, one had not presented clinical improvement with a pentavalent antimonial, and one had suffered a relapse after healing obtained with the use of pentamidine isothionate. The interval between treatments (more than 1 y) does not permit the hypothesis of a favorable response affected by the schedules previously used. This fact suggests the possible effectiveness of itraconazole in patients refractory to other treatments.

Although there are reports in the literature of patients who achieved spontaneous MCL healing without any specific treatment, this event is unlikely to have occurred in the present patients whose lesions healed after itraconazole treatment, since these patients presented active disease as determined by otorhinolaryngologic examination at the beginning of treatment with this medication.[4,34]

In the present study there was no apparent difference in the therapeutic response of severe cases of the disease, considered to be patients with perforation of the nasal septum or involvement of the oral mucosa, since the lesions healed in four of these six patients, as compared to two of four patients with moderate involvement (no perforation of the nasal septum).

The reason that the lesions healed in six patients whereas the remainig four patients did not respond to itraconazole treatment in this pilot study is unknown; also unresolved are questions with respect to treatment failure of other medications for MCL, such as pentavalent antimonials, drugs that have been used since the late forties and whose effects have been reported in a much larger number of studies on leishmaniasis.[35] Theoretically, treatment failure could be attributed to factors related to the parasite and to host immunity.[7,36,37] It has been demonstrated that the therapeutic response depends on the leishmanial strain, with *L. braziliensis* being less sensitive to pentavalent antimonials than *Leishmania mexicana*.[38] It has also been questioned whether cases of a lack of response to antimonials are attributable to the resistance of *Leishmania* or to a deficient host immune response, since a *Leishmania donovani* strain from a patient who did not respond to treatment with N-methylglucamine antimoniate, sodium stibogluconate in combination with allopurinol, amphotericin B, and pentamidine was susceptible in marmosets submitted to the same treatment regimen as the patient.[39] Future studies on itraconazole assessing treatment failure associated with parasites resistant to the medication or with immunologic parameters of the host would be helpful to clarify why some patients with MCL respond to treatment and others do not.

In the present study, all the hematologic parameters and the hepatic enzymes remained at normal levels, suggesting that this drug may be useful for patients for whom habitual medications are contraindicated. The recurrent characteristics of this clinical form require follow-up.[14] Over a mean period of 14.5 months (range, 12-18 mo) of post-treatment follow-up, no patient presented reactivation of the disease.

The authors have no knowledge of any other study on the use of itraconazole for treating MCL; therefore, even though this study was conducted on only 10 patients, it is important for showing the usefulness of itraconazole for treatment of MCL. This drug is administered orally and has low toxicity so that it is suitable for the epidemiologic reality of MCL in rural and periurban areas, contrasting to the high cost and toxicity of standard intravenous treatment. The present phase II pilot study should be followed by a randomized, double blind controlled trial to clarify the benefits of itraconazole in MCL.

REFERENCES

1. World Health Organization. Report of Expert Committee on the control of leishmaniasis. Technical Report Series 793. Geneve: WHO, 1990.
2. Marzochi MCA, Marzochi KBF. Tegmentary and visceral leishmaniasis in Brazil: emerging anthropozoonosis and possibilities for their control. Cad Saude Publica 1994; 10(Suppl 2):359-375.
3. Grimaldi G Jr, Tesh RB. Leishmaniasis of the New World: current concepts and implications for future research. Clin Microbiol Rev 1993; 6:230-250.
4. Marsdsen PD. Mucosal leishmaniasis (espundia Escomel, 1911). Trans R Soc Trop Med Hyg 1984; 78:561-562.
5. Amato VS, Boulos MI, Amato Neto V, Filomeno LT. The use of a silicone T tube in the treatment of a case of American

mucocutaneous leishmaniasis with tracheomalacia. Rev Soc Bras Med Trop 1995; 28:129-130.
6. Franke ED, Wigwall S, Cruz ME, et al. Efficacy and toxicity of sodium stibogluconate for mucosal leishmaniasis. Ann Intern Med 1990; 113:934-940.
7. Berman JD. Human leishmaniasis: clinical, diagnostic, and chemotherapeutic developments in the last 10 years. Clin Infect Dis 1997; 24:684-703.
8. Sampaio RNR, Marsden PD. Treatment of the mucosal form of leishmaniasis without response to glucantime, with liposomal amphotericin B. Rev Soc Bras Med Trop 1997; 30:125-128.
9. Romero GAS, Lessa HA, Macedo VO, et al. Open therapeutic study with aminosidine sulfate in mucosal leishmaniasis caused by *Leishmania (Viannia) braziliensis*. Rev Soc Bras Med Trop 1996; 29:557-565.
10. Llanos-Cuentas A, Echevarria J, Cruz M, et al. Efficacy of sodium stibogluconate alone and in combination with allopurinol for treatment of mucocutaneous leishmaniasis. Clin Infect Dis 1997; 25:677-684.
11. Falcoff E, Taranto NJ, Remondegui DE, et al. Clinical healing of antimony-resistant cutaneous or mucocutaneous leishmaniasis following the combined administration of interferon-γ and pentavalent antimonial compounds. Trans R Soc Trop Med Hyg 1994; 88:95-97.
12. Berman JD Activity of imidazoles against *Leishmania tropica* in human macrophages cultures. Am J Trop Med Hyg 1981; 30:566-569.
13. Dogra J, Saxena VN, Jaipur CGHS. Itraconazole and leishmaniasis: a randomized double blind trial in cutaneous disease. Int J Parasitol 1996; 26:1413-1415.
14. Netto EM, Marsden PD, Llanos-Cuentas A, et al. Long-term follow-up of patients with *Leishmania (Viannia) braziliensis* infection and treated with glucantime. Trans R Soc Trop Med Hyg 1990; 84:367-370.
15. Borelli D. A clinical trial of itraconazole in the treatment of deep mycosis and leishmaniasis. Rev Infect Dis 1987; 9:57-63.
16. Saenz RE, de Rodriguez CG, Johnson CM, et al. Efficacy and toxicity of pentostam against Panamanian mucosal leishmaniasis. Am J Trop Med Hyg 1991; 44:394-398.
17. Franke ED, Llanos-Cuentas A, Echevarria JE, et al. Efficacy of 28-day and 40-day regimens of sodium stibogluconate in the treatment of mucosal leishmaniasis. Am J Trop Med Hyg 1994; 51:77-82.
18. Pradinaud R, Servans G, Sainta Marie D, et al. Bilan de 10 années de traitement de la leishmaniose tegumentare par la pentamidine en Guyane Française: à propos de 1025 cas. Nouv Derm 1991; 10:456-461.
19. Wortmann GW, Frases SL, Arenson NE, et al. Failure of amphotericin B lipid complex in treatment of cutaneous leishmaniasis. Clin Infect Dis 1998; 26:1006-1007.
20. Amato V, Amato J, Nicodemo A, et al. Traitement par iséthionate de pentamidine de la leishmaniose muqueuse. Ann Dermatol Venereol 1998; 125:492-495.
21. Hart DT, Cauwers WJ, Willemsens G, et al. Perturbation of sterol biosynthesis by itraconazole in *Leishmania mexicana mexicana* infected macrophages. Mol Biochem Parasitol 1989; 33:123-134.
22. Akuffo H, Dietz M, Teklemaniam S, et al. The use of itraconazole in the treatment of leishmaniasis caused by *Leishmania aethiopica*. Trans R Soc Trop Med Hyg 1990; 84:532-534.
23. Larosa E, Cauwenbergh G, Cilli P, et al. Itraconazole pharmacokinetics in female genital tract: plasma and tissue levels in patients undergoing hysterectomy after a single dose of 200 mg itraconazole. Eur J Obstet Gynecol Reprod Biol 1986; 23:85-89.
24. Al Fouzan AS, Al Saleh QA, Najem NM, et al. Cutaneous leishmaniasis in Kuwait: clinical experience with itraconazole. Int J Dermatol 1991; 30:519-521.
25. Momeni AZ, Jalayer T, Eman Jomeh M, et al. Treatment of cutaneous leishmaniasis with itraconazole. Randomized double blind study. Arch Dermatol 1996; 132:784-786.
26. Amato VS, Duarte MIS, Nicodemo AC, et al. An evaluation of clinical, serologic, anatomopathologic, and immunohistochemical findings for fifteen patients with mucosal leishmaniasis before and after treatment. Rev Inst Med Trop Sao Paulo 1998; 40:23-30.
27. Bittencourt AL, Barral A. Evaluation of the histopathological classifications of American cutaneous and mucocutaneous leishmaniasis. Mem Inst Oswaldo Cruz 1991; 86:51-56.
28. Sotto MN, Yamashiro-Kanashiro EH, Matta VLR, et al. Cutaneous leishmaniasis of New World: diagnostic immunopathology and antigen pathways in skin and mucosa. Acta Tropica 1989; 46:121-130.
29. Singer C, Armstrong D, Jones TC, et al. Imported mucocutaneous leishmaniasis in New York City. Am J Med 1975; 59:444-447.
30. Aebischer T. Recurrent cutaneous leishmaniasis: A role for persistent parasites? Parasitology Today 1994; 10:25-28.
31. Oliveira MRF, Macêdo VO, Carvalho EM, et al. An evolutionary study of mucosal leishmaniasis (a 7- to 17-year follow-up) due to *Leishmania (Viannia) braziliensis* in Três Braços, Bahia. Rev Soc Bras Med Trop 1995; 28:325-332.
32. Lainson R. Leishmaniasis. In: Steele JH, ed. Handbook of zoonoses. Florida: CRC Press, 1982:41-103.
33. Cuba CC, Llanos-Cuentas EL, Barreto AC, et al. Human mucocutaneous leishmaniasis in Três Braços, Bahia, Brazil. An area of *Leishmania braziliensis braziliensis* transmission. I. Laboratory diagnosis. Rev Soc Bras Med Trop 1984; 17:161-167.
34. Marsden PD, Badaro R, Netto EM, Casler JD. Spontaneous clinical resolution without specific treatment in mucosal leishmaniasis. Trans R Soc Trop Med Hyg 1991; 85:221.
35. Marsden PD. Pentavalent antimonials: old drugs for new diseases. Rev Soc Bras Med Trop 1985; 18:187-195.
36. Manson-Bahr PEC. East African kala-azar with special reference to the pathology, prophylaxis, and treatment. Trans R Soc Trop Med Hyg 1959; 53:123-137.
37. Bryceson ADM, Chulay JD, Mugambi M, et al. Visceral leishmaniasis unresponsive to antimonial drugs. II. Response to high-dosage sodium stibogluconate or prolonged treatment with pentamidine. Trans R Soc Trop Med Hyg 1985; 79:705-714.
38. Marzochi MCA. Leishmanioses no Brasil. R Bras Med 1992; 63:82-104.
39. Dietze R, Araujo RC, Lima MLR, et al. Ensaio terapêutico com Glucantime em saguis (*Callithrix jacchus*) infectados com uma cepa de *Leishmania donovani* aparentemente resistente ao tratamento. Rev Soc Bras Med Trop 1985; 18:39-42.